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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,375	03/21/2000	SUSAN MARY KINGSMAN	DYOU23.001AP	9861

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EXAMINER	
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ART UNIT	PAPER NUMBER
	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)
	09/445,375	KINGSMAN ET AL.
	Examiner	Art Unit
	J. Eric Angell	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-16,18-21,24,25,27-29,31-34,36-38,41-43,45-58 and 60-74* is/are pending in the application.

4a) Of the above claim(s) *41-43,45 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-16,18-21,24,25,27-29,31-34,36-38,47-53,57,58 and 61-74* is/are rejected.

7)☒ Claim(s) *54-56 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 12/24/02, as Paper No. 22. Claim 1 has been amended. Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 41-43, 45-58 and 60-74 are pending in the application and are addressed herein.

2. Claims 41-43, 45 and 46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, for the reasons of record.

3. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

4. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

5. Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 47-58 and 60-74 are examined herein.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim recites the phrase, "to a selective tumor site". This recitation

renders the claim indefinite because it is unclear what a "selective tumor site" is, as it is not defined in the specification.

8. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because: claim 38 recites the phrase, "using a vector according to claim 1 to deliver the polynucleotide to a first cell..." (Emphasis added). This phrase renders the claim indefinite because claim 1 is drawn to two polynucleotides, one encoding tumor interacting protein, and a second polynucleotide of interest. Therefore, it is unclear if "the polypeptide" of claim 38 refers to the polynucleotide encoding a tumor interacting protein, or to the second polynucleotide of interest.

9. Claims 54-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 54-56 are drawn to the method of claim 30; however, claim 30 has been cancelled. Therefore, the claims are indefinite because the method to which the claims refer is unclear. Claims 54-56 are withdrawn from further consideration.

10. Claims 61-64 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 61 recites the phrase, "a vector comprising a polynucleotide encoding a tumor interacting protein wherein the tumor interacting protein recognizes a tumor and wherein

the vector delivers a second polynucleotide of interest to the tumor". This phrase renders the claims indefinite because it appears that the vector delivers the second polynucleotide to the tumor recognized by the tumor interacting protein.

11. Claims 25, 33, 58, 68, 70, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Specifically, for claims 25 and 68, the omitted steps are: transplanting the ex vivo transfected cells back into the mammal. The instant claims are drawn to a method of treating cancer in a mammal by delivering a polynucleotide of interest ex vivo to a tumor. It is noted that the only way to treat cancer in a mammal by delivering a vector ex vivo to a tumor is by transplanting the ex vivo cells into the mammal comprising the tumor. It is not clear how delivering a polynucleotide of interest to a cell ex vivo (i.e. outside of the body) would have any effect on a tumor in vivo (inside the body) without transplanting the transduced cell back in to the mammal.

Claims 33 and 73 encompass a method of treating cancer in a mammal comprising administering a combination of a cytokine or cytokine encoding gene and one or more genes encoding a tumor interacting protein. The omitted step(s) in these claims are: incorporating the genes encoding the polypeptides of interest into a vector. Unless the genes are in a vector, it is unclear how the genes would express the encoded polypeptides a vector comprising the proper regulatory elements (such as a promoter) is required for gene expression. Claims 58 and 74 are dependent claims and are rejected for the same reasons.

Claims 70 is drawn to a method for delivering a polynucleotide sequence to a second cell neighboring a first cell comprising using a vector to deliver the polynucleotide to said first cell wherein the vector delivers a second polynucleotide of interest to a tumor. The omitted step(s) in this claim are: indicating that the first and second polynucleotides are present in the same vector. A vector which delivers a first polynucleotide and a second polynucleotide to cells must comprise both the first and second polynucleotide sequences; otherwise it would be unclear how a vector could deliver a first and second polynucleotide sequence to cells.

Claim Rejections - 35 USC § 112, first paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 47-53, 57, 58 and 60-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vector comprising a polynucleotide encoding a tumor interacting protein. The tumor interacting protein can be a protein which binds to a trophoblast cell surface antigen. The only tumor interacting protein which binds to a trophoblast cell surface antigen is an antibody specific for the trophoblast antigen 5T4. Therefore, the claims encompass a genus of tumor interacting proteins for which there is insufficient written description provided.

The Written Description Guidelines for examination of patent applications indicates that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice; or by disclosure of relevant, identifying characteristics (i.e. structure or other physical and/or other chemical properties); by functional characteristics coupled with a known or disclosed correlation between function and structure; or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. (See MPEP 2100-164).

In the instant case, the claims encompass a huge genus of molecules considering: 1) every possible trophoblast cell surface antigen that could be expressed on a tumor cell, including antigens which have not yet been identified; and 2) every possible tumor interacting protein which could bind to each of the trophoblast cell surface antigens. The specification discloses a number of molecules that are known to be tumor antigens, such as those listed on page 6 of the specification (see lines 8-22). However, none of the antigens listed on page 6 are known to be trophoblast cell surface antigens. The specification only describes one trophoblast cell surface antigen expressed on the surface of tumor cells, the 5T4 antigen. Furthermore, the specification only discloses one tumor interacting protein which binds to a trophoblast cell surface antigen - an antibody which binds to the 5T4 antigen. The specification does not disclose any relevant, identifying characteristics (such as structure or physical/chemical properties) or any structure-function relationship of the 5T4 antigen which are possessed by all trophoblast cell surface antigens encompassed by the claims, nor does the specification indicate any molecules other than antibodies which would bind to any of the trophoblast cell surface antigens. Therefore, the

specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 47-53, 57, 58 and 60-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the growth of a tumor in a mammal wherein said method comprises directly administering to said tumor a vector comprising a polynucleotide which encodes and expresses an antibody that binds to a 5T4 trophoblast surface antigen and an antitumor gene;

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted the instant claims are drawn to a product (a vector or gene delivery system comprising a vector) as well as methods of making and using the product (such as delivering the vector to a tumor and treating cancer). However, the only "real world" use contemplated for the vector/delivery system is for treating cancer. Therefore, the enablement rejection is appropriate for all of the claims as one of skill in the art would not know how to use the product for its intended use (treating cancer) without first completing additional experimentation in order to over come the problems associated with using the product for gene therapy.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a product (a vector or gene delivery system) and methods of using the product to treat cancer. Therefore the general nature of the invention is gene therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass a vector or any gene delivery system which comprises a polynucleotide encoding any tumor interacting protein which binds to a trophoblast cell surface antigen and a second polynucleotide of interest. It is noted that claims 61-74 encompass a vector comprising a polynucleotide encoding any tumor interacting protein – these broad claims encompass tumor interacting proteins specific for a trophoblast cell surface antigen. As mentioned above in the written description rejection, the claims encompass a huge genus of tumor interacting proteins considering every possible trophoblast surface antigen which could bind to a trophoblast cell surface antigen and every molecule which could interact with each of the trophoblast surface antigens encompassed by the

claims. Furthermore, the claims encompass treating cancer in a mammal by systemic and ex vivo administration as well as direct administration of the vector to a tumor in a mammal.

The unpredictability of the art and the state of the prior art

As mentioned above, the claims encompass a vector comprising a polynucleotide encoding any tumor interacting protein which binds to a trophoblast cell surface antigen. However, the specification only discloses one species of the claimed genus. Without a clear description of the genus of tumor interacting proteins encompassed by the claims, one of skill in the art could not know which molecules are and which are not tumor interacting proteins specific for a trophoblast cell surface antigen (other than the one described). Therefore, one of skill in the art could not be able to reasonably predict which molecules could be successfully used in the claimed invention.

Regarding gene therapy, Anderson (1998) (as mentioned in the previous Office Action) teaches, "[S]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered... the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defences can be overcome, and how to manufacture efficiently the vectors that we do make" (see page 30 under Conclusion).

Greco et al. (Frontiers in Biosci. 2002; 7:d1516-1524) also indicates some of the problems associated with cancer gene therapy. Specifically, Greco teaches,

> Gene therapy for cancer treatment represents a promising approach that has shown selectivity and efficacy in experimental systems as well as clinical trials. Some major problems remain to be solved before this strategy becomes routinely adopted in the clinic, one of the main challenges being the improvement in gene delivery... The 'magic' vector

> should be targeted, protected from degradation, and immune attack, and safe for the recipient and the environment. Moreover it should express the therapeutic gene for as long as required, in an appropriately regulated fashion (See page 1516, first column. The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported with naked DNA, efficient delivery has been restricted to intratumoral injection (see p. 1517, paragraph bridging columns 1 and 2)... The efficient delivery of DNA to tumor sites remains a formidable task, but progress has been made in recent years using both viral and non-viral methods (see p. 1517, column 2).

Regarding the use of retroviral vectors for cancer gene therapy, Greco teaches,

> [T]he major limitation for retroviral vehicles, for example those derived from the murine leukemia virus (MoMLV), is that the target cells must be proliferating at the time of infection. Retroviral vectors are therefore, more suited for ex vivo gene therapy, in which isolated cells are propagated in culture, transduced and subsequently transplanted into a recipient patient (See p. 1517, last paragraph). In clinical trials, safety has been demonstrated, but transfection efficiencies were rather low. These results may be due to the slower growth rate of spontaneous human malignancies compared to experimental rodent tumors, in which this strategy was initially tested. (See p. 1518. first paragraph).

The claims also encompass ex vivo gene therapy methods. It is noted that that at the time of invention the only vectors used in ex vivo gene therapy protocols were retroviral vectors. However, it is recognized in the art that cells that have been modified to express novel proteins can induce an immune response against the cells expressing the novel protein. For instance, Riddell et al. (Nature Medicine, 1996; 2:216-221) teaches,

> A potential obstacle to gene therapy is the elimination of such gene-modified cells by an immune response to novel protein products of the introduced genes... [F]ive or six patients (administered cytotoxic T cells modified by retroviral transduction to express a gene permitting positive and negative selection) developed cytotoxic T-lymphocyte responses specific for the novel protein and eliminated the transduced cytotoxic T cells. The rejection of genetically modified cells by these immunocompromised hosts suggests that strategies to render gene-modified cells less susceptible to host immune surveillance will be required for successful gene therapy. (See p. 216, abstract).

The claims also encompass treating cancer cells of the hematopoietic cell lineage. The main vectors used to transfect hematopoietic cells at the time of invention were retroviral

vectors. However, retroviral vectors were known to transfect human hematopoietic cells with low efficiency. For instance, Richter (Int. Journ. Hematology, 2001:73:162-169) teaches,

> Oncoretroviral vectors have been the main vectors used for hematopoietic stem cells (HSCs) because of their ability to integrate into the chromosome of their target cells. Gene-transfer efficiency of murine HSCs is high using oncoretroviral vectors. In contrast, gene-transfer efficiency using the same viral vectors to transduce human HSCs or HSCs from large animals has been much lower. Although these difficulties may have several causes, the main reason for the low efficiency of human HSC transduction with oncoretroviral vectors is probably because of the non-dividing nature of the HSCs.

Working Examples and Guidance Provided

The specification does not disclose any evidence that the vectors can deliver the polynucleotide(s) to cancer cells in vivo by systemic administration. Examples 3, 4, 7, 8 and 9 indicate possible ways that the vector and method could possibly be used, however, these examples are only prophetic and do not disclose any results indicating that the methods would have any therapeutic effect. Applicants have provided a declaration of one of the inventors, Dr. Miles Carroll, which demonstrates;

a) Intratumoral delivery of adenoviral vectors encoding scFv proteins specific to 5T4, and expression therefrom in mice;

b) Specific expression of B7-scFv in the sera of Balb/c mice;

c) Expression of a B7-scFv in a tumor following intratumoral delivery using the AdB7-scFv vector in mice;

d) The scFv-Hγ1 fusion protein is able to direct cytotoxicity against cells expressing the 5T4 antigen at the cell surface, wherein the targeted cells are *in vitro*;

e) The genetic delivery of a construct encoding the scFv- Hγ1 fusion protein using the MLV-LscFV Hγ1 to cancer cells leads to secretion of the protein from the cells and their binding back to the cell surface, wherein the cells are *in vitro*.

Therefore, the declaration indicates that the vector and methods of using the vector can deliver a gene of interest to a tumor by direct injection of the vector into the tumor. Furthermore, the declaration indicates that the vector can deliver an antitumor gene to cancer cells in vitro, resulting in an antitumor effect in the transduced cells. However, there is no indication that the vector can be systemically delivered to a subject and result in the specific transduction of a cancer cell and result in an anti-cancer effect. Considering the unpredictable nature of systemic delivery of a gene therapy vehicle to cancer cells in vivo including specificity of delivery, degradation and immune attack, one of skill in the art would not be able to use the claimed invention with a reasonable expectation of success without performing additional experimentation to overcome the problems recognized in the art for cancer gene therapy by systemic administration.

Quantity of Experimentation

Additional experimentation is required in order to use the claimed invention to the full scope encompassed by the claims with a reasonable expectation of success.

First, considering the large genus of tumor interacting proteins encompassed by the claims, additional experimentation would have to be done in order to be able identify the tumor interacting molecules encompassed by the claims. As mentioned above, the claims encompass a large number of tumor interacting proteins considering every possible trophoblast cell surface antigen and every molecule which could interact with each of the trophoblast cell surface

antigens. The specification has only identified one molecule which interacts with one specific trophoblast cell surface antigen.

Second, considering the art-recognized problems associated with systemic delivery of gene therapy vehicles for the treatment of disease such as cancer (mentioned above), additional experimentation would have to be done to overcome problems such as specific delivery, degradation, immune attack, and appropriate expression of the therapeutic gene. The relevant art recognizes that overcoming these obstacles are crucial for in vivo cancer gene therapy by systemic administration of the therapeutic vector.

Level of the skill in the art

The level of the skill in the art is deemed to be high considering the highly technical nature of gene therapy.

Conclusion

Considering the large genus of tumor interacting proteins encompassed by the claims, the unpredictable nature of in vivo gene therapy by systemic administration, the lack of working examples and guidance in the specification regarding 1) identifying the large genus of tumor interacting proteins encompassed by the claims and 2) the use of the vectors for in vivo gene therapy by systemic administration; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention with a reasonable expectation of success is undue.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-10, 12-16, 18, 20, 24, 27, 28, 33, 34, 36, 37, 47-53, 58, 60-65, and 71-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 96/30504) in view of Myers et al. (JBC Vol. 269, No. 12: p. 9319-9324; 1994).

Anderson teaches a retroviral vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor interacting protein is targeted (i.e. binds) to a specific tumor cell type, and delivers a second polynucleotide of interest (e.g. a therapeutic product) to the interior of the tumor cell (e.g., see abstract; p. 1, paragraphs 1-2; p. 19, second paragraph; and paragraph bridging p. 20-21); wherein the vector delivers a second polynucleotide of interest which is a therapeutic polynucleotide encoding a cytokine such as Tumor Necrosis Factors, Interferons, and Interleukins, (p. 21, second paragraph, and p. 14, lines 7-13); wherein the polynucleotide comprises at least one tumor binding domain (i.e. a tumor binding protein, such

as an antibody or part of an antibody) which binds with a tumor cell-associated surface molecule that is expressed on one cell type (here an antibody to erb-2, known in the are to be expressed on breast tumor cells; see paragraph bridging p. 7-8); and wherein the vector can be used for *in vivo* delivery of polynucleotide/product of interest (e.g. p. 2, second paragraph). Anderson teaches that the vector is useful for treating cancer (see page 20, last paragraph).

Anderson also teaches that the tumor interacting protein can be expressed as a fusion protein to a product of interest (here, the targeting polypeptide expressed as a fusion protein with specific envelope proteins, such as SEQ ID NOS: 1-5 (e.g., see last paragraph, p.3 through first paragraph, p. 7); and that the envelope proteins includes a secretory signal or "leader" sequence, thus making the fusion protein a secretory protein (i.e. secreted) (see paragraph bridging p. 6-7).

Anderson does not specifically teach a vector that binds to a trophoblast cell surface antigen, or that the trophoblast cell surface antigen to which the vector binds is 5T4.

Myers teaches the isolation of a cDNA encoding 5T4 Oncofetal Trophoblast Glycoprotein, and indicates that 5T4 (identified by a monoclonal antibody) has been shown to be "strongly expressed on fetal trophoblast membranes, but absent from most normal non-pregnant tissues with a few epithelia [being] weakly positive" and "is expressed by a wide variety of transformed embryonic and carcinoma-derived cell lines and many different human carcinomas." (See p. 9319, paragraph bridging columns 1 and 2), and can be used to target therapeutic molecules to several types of solid tumors, as evidenced by Forsberg et al. (JBC, Vol. 272 No. 19: 12430-12436; 1997).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the vector taught by Anderson with a substituted tumor

interacting protein, wherein the substituted tumor interacting protein is the antibody (or part thereof) that specifically interacts with 5T4 taught by Myers, to create the vector of the instant claims with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by Anderson, who teaches "retroviruses can be made 'targetable' to a specific type of cell if a portion of the receptor binding region is modified such that the receptor binding region includes a polypeptide which binds to a ligand or receptor of a target cell" and mentions many different specific examples (see middle of p. 7 through the end of p. 8) including "antibodies and fragments thereof, including single chain antibodies" (see paragraph bridging p. 7-8).

4. Claims 1, 18, 19, 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 96/30504) in view of Myers et al. (JBC Vol. 269, No. 12: p. 9319-9324; 1994) and further in view of Barber (U.S Patent 5,591,692; 1997).

Anderson teaches a retroviral vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor interacting protein is targeted (i.e. binds) to a specific tumor cell type, and delivers a second polynucleotide of interest (e.g. a therapeutic product) to the interior of the tumor cell (e.g., see abstract; p. 1, paragraphs 1-2; p. 19, second paragraph; and paragraph bridging p. 20-21); wherein the vector delivers a second polynucleotide of interest which is a therapeutic polynucleotide (p. 21, second paragraph); wherein the polynucleotide comprises at least one tumor binding domain (i.e. a tumor binding protein, such as an antibody or part of an antibody) which binds with a tumor cell-associated surface molecule that is expressed on one cell type (here an antibody to erb-2, known in the are to be expressed on breast tumor

cells; see paragraph bridging p. 7-8); and wherein the vector can be used for *in vivo* delivery of polynucleotide/product of interest (e.g. p. 2, second paragraph).

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Neither Anderson nor Myers teaches that the retroviral vector further comprises tumor specific promoter.

Barber teaches a recombinant retroviral vector which can be targeted to preselected cell lines and wherein the vector comprises tissue-specific promoters such as tumor-specific

promoters (e.g., transferring receptor or Thymidine kinase; see column 4, lines 1-10 and column 21, line 12 through column 22 line 21).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Anderson and Myers (as mentioned above) with the teachings of Barber to create the vector of the instant claims with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by Anderson, who teaches the retroviral vector may further comprise a sequence encoding a therapeutic agent under the control of a suitable promoter (see paragraph bridging pages 13 and 14 and p. 15, second paragraph), and can be used to treat tumors (see paragraph bridging p. 20-21), thus indicating that expression of the therapeutic agent in tumor cells would be desirable.

Response to Arguments

Applicants argued that the previous rejection of claims under 35 USC 112, first paragraph was inappropriate considering the declaration filed April 30, 2002, which indicated 1) successful delivery of a vector encompassed by the claims which expressed a reporter gene by direct injection (i.e. intratumoral delivery), and 2) a vector encompassed by the claims which expressed a scFV-Hγ1 fusion protein resulted in a directed cytotoxic effect against cells expressing the 5T4 antigen in vitro and 3) and binding of the scFV1 to the cells in vitro.

In response, it is noted that the rejection was against using the claim vector as a treatment for cancer by delivering the vector by any means (systemic or direct administration, etc.). The declaration does indicate a vector encompassed by the claims can be delivered to tumor cells in a

mammal only by direct administration of the vector to the tumor by direct intratumoral delivery of the vector. However, the declaration does not indicate that the vector be successfully administered to cancer cells in a mammal by any other method other than direct intratumoral delivery of the vector. Therefore, the claims are only enabled for direct intratumoral delivery of the vector as set forth above.

Applicants argued that the rejection of claims under 35 USC 103(a) as being unpatentable over Anderson in view of Myers is inappropriate because the combination of Anderson and Myers is not sufficient to provide one of ordinary skill in the art with the teaching and motivation to make and use the presently claimed invention. It is noted that applicants argue against the teachings of Forsberg. It is respectfully pointed out that the claims were rejected as being unpatentable over Anderson and Myers only, not Forsberg. Therefore, the arguments regarding the teaching of Forsberg are irrelevant to the pending rejections. With respect to arguments as they pertain to Anderson and Myers, Applicants argue that Anderson does not contemplate a vector encoding a tumor interacting protein specific for a the trophoblast 5T4 antigen, nor does Anderson provide motivation to use a tumor interacting protein specific for a the trophoblast 5T4 antigen. It is acknowledged that Anderson does not specifically teach a tumor interacting protein specific for the trophoblast 5T4 antigen. However, Anderson does teach a retroviral vector which encodes a tumor interacting protein, as mentioned in the previous Office Action, and reiterated above. The teaching of a vector encoding a tumor interacting protein wherein the tumor interacting protein can be a number of different molecules including polypeptides (such as antibodies or fragments thereof including single chain antibodies) which bind to a ligand or a

receptor on a target cell (see Anderson p. 7, lines 20-39 and p. 8) which provides motivation for using any polypeptide which binds to any ligand or receptor on the target cell. Myers teaches an antibody that specifically binds to the trophoblast cell surface antigen 5T4, and teaches "5T4 is a human oncotrophoblast antigen expressed in a variety of carcinomas but with a restricted pattern of expression in normal adult tissues" (See abstract). Therefore, Myers teaches 5T4 was a trophoblast cell surface antigen that is expressed in tumor cells and teaches an antibody which specifically interacts with 5T4. Therefore, Anderson and Myers teach all of the limitations of the rejected claims, and Anderson provides motivation for combining the references (see previous Office Action and above).

5. Applicants argue that the rejection of claims under 35 USC 103(a) as being unpatentable over Anderson in view of Myers and Barber is not appropriate. Applicants contend that a prima facie case of obvious has not been provided, and asserts that the rejection is based on four references. First, it is respectfully pointed out that the rejection is based only on three references Anderson, Myers and Barber, not four references. It is also respectfully pointed out that the rejection is not based on Forsberg, as asserted in the Applicants arguments. Therefore, the arguments regarding the teaching of Forsberg are irrelevant to the pending rejections. Furthermore, the teachings of Anderson, Myers and Barber can be used to make a prima facie case of obviousness for the reasons of record and above. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

The objection to the drawings has been withdrawn in view of newly submitted drawings.

The double patenting rejection has been withdrawn in view of the cancellation of claim 59.

Conclusion

No claim is allowed.

It is pointed out that new grounds of rejection have been added; therefore, the instant rejection is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
January 26, 2003